Complete Summary

GUIDELINE TITLE

Erlotinib for the treatment of non-small-cell lung cancer.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Erlotinib for the treatment of non-small-cell-lung cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Nov. 26 p. (Technology appraisal; no. 87).

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 8, 2009 - Tarceva (erlotinib): OSI Pharmaceuticals, Inc., Genentech and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of new safety information added to the WARNINGS AND PRECAUTIONS sections of the prescribing information for Tarceva. Gastrointestinal perforation (including fatalities), bullous, blistering and exfoliative skin conditions including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, in some cases fatal, and ocular disorders, including corneal perforation or ulceration have been reported during use of Tarceva.
- September 23, 2008 - Tarceva (erlotinib): OSI Pharmaceuticals and Genentech notified healthcare professionals that cases of hepatic failure and hepatorenal syndrome, including fatalities, have been reported during use of Tarceva, particularly in patients with baseline hepatic impairment. New information has been provided in the revised prescribing information, and other recommendations are included in the WARNINGS and DOSAGE AND ADMINISTRATION sections.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Non-small-cell lung cancer (NSCLC)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Oncology
Pulmonary Medicine

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the clinical effectiveness and cost effectiveness of erlotinib for the treatment of non-small-cell lung cancer (NSCLC)

TARGET POPULATION

Adults with locally advanced or metastatic (stage III/IV) non-small cell lung cancer (NSCLC) who have failed at least one prior chemotherapy regimen

INTERVENTIONS AND PRACTICES CONSIDERED

Erlotinib as a second-line treatment

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Overall survival

    - Progression-free survival
    - Overall survival rates (partial and complete)
    - Duration of response
    - Toxic effects
    - Quality of life
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Search Strategy

Appropriate databases and conference proceedings were searched. Search terms for electronic databases included a combination of free-text and index terms combined with drug names used as free-text terms. The ERG was unable to reproduce these searches as sufficient detail (e.g. specific search strategies used for each database and the numbers of references retrieved for each search) was not provided in the submission.

In addition to these searches, it is stated that the study report from the key licensing study for erlotinib, BR21, obtained from the Roche Regulatory Affairs Department, was used as a further data source.

The search strategy conducted by the ERG confirms the finding of only one relevant direct comparison trial. However, the indirect comparison search conducted by the ERG identified a further randomised controlled trial (RCT), investigating the use of docetaxel given every three weeks compared with a weekly schedule administered as a second-line therapy in 125 patients with advanced non-small-cell lung cancer (NSCLC).

Inclusion and Exclusion Criteria

Details of inclusion and exclusion criteria are provided in Table 3-2 of the ERG report (see the "Availability of Companion Documents" field) and are considered appropriate and complete.

Application of Inclusion Criteria

Application of inclusion criteria (e.g., the number of reviewers involved in the process and whether this was done independently) was not defined in the submission.

Flow diagrams and tables of included trials are presented in the submission for both reviews. For searches of trials which include direct comparisons of erlotinib, the inclusion criteria were applied to 14 publications. A total of five publications describing one RCT were included in the review. For searches of studies relevant to the indirect comparison of erlotinib and docetaxel, 48 publications were identified and 24 were included in the company submission.

Cost-Effectiveness

Summary of Published Cost-Effectiveness Studies Identified in the Submission

Identification and Description of Studies

The submission did not fully describe the details of the electronic search strategy. The ERG was therefore unable to replicate the electronic searches undertaken by the company. However, key terms used and databases searched were described. The number of papers initially found and the number of papers excluded from the review were not reported.

Stated inclusion criteria were:

Date of Publication

Studies published after January 1st 1996 were included.

Language of Publication

Only studies published in English or where English translations were available were included in the systematic review.

Type of Study and Outcome

Studies were included if they described an economic evaluation quantifying both costs and benefits.

Intervention

Studies that examined the second-line treatment of NSCLC with docetaxel or erlotinib were included. However due to lack of data, studies that evaluated the use of docetaxel in first-line were also included as well as some general costing studies on lung cancer.

Subjects

Studies examining patients with lung cancer were included. No restrictions were placed on the age or gender of patients included in the analysis. Economic evaluations conducted on patients with different levels of disease severity were also included if they assessed cost-effectiveness in a subgroup of patients with early disease.

Using these inclusion criteria, the company identified 10 studies for inclusion in the review. However, by including the criterion "some general costing studies on lung cancer" the company's inclusion criteria becomes disorderly. Under the heading "type of study and outcome", studies are to be included if they describe both costs and benefits. To then allow general costing studies on lung cancer to be included only serves to confuse eligibility as the type of costing/economic study to be included in the review becomes undefined. It is not then possible to determine whether or not all relevant studies are included in the review, as there are many studies which could be considered relevant under the title "general costing studies on lung cancer".

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

One direct comparison randomized controlled trial (RCT) and eleven indirect comparison RCTs were included.

Cost-Effectiveness

Ten studies were identified for inclusion in the review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Liverpool Reviews and Implementation Group (LRiG) (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Quality Assessment

Direct Comparison

The company submission did not include a formal quality assessment, or discuss the methodological limitations of the one included trial (BR21). However, the submission provides information concerning certain aspects of the methodological quality of the included trial including the randomisation procedure and the adequacy of follow up.

As the randomisation process was performed centrally, it is likely that allocation concealment was adequate. Baseline characteristics were generally comparable in each treatment arm.

The nature of blinding was not explicitly reported in the submission or in the published paper; but, as this was a double-blind trial, it is likely that both participants and investigators were kept blind to treatment assignment. No information on blinding of the outcome assessors was provided. However, due to the large proportion of patients in the erlotinib arm who developed a rash, blinding may well have been compromised as it may have been apparent to both participants and investigators who had been randomised to the erlotinib arm of the trial. This might be irrelevant for the measurement of the primary endpoint (overall survival) but needs to be considered when analysing key secondary outcomes (progression-free survival, objective response and quality of life).

Indirect Comparison

The company submission did not provide any quality assessment of the studies included in the indirect comparison of erlotinib versus docetaxel.

Data Extraction

Details of the data extraction process (e.g., number of reviewers and whether data were extracted independently) were not provided in the submission.

Cost-Effectiveness

Data Extraction

The company extracted data from the 10 papers included in the review including the aim of the study, the study results, and relevance to decision making in England and Wales. This data extraction is simplistic and does not provide sufficient detail for a comprehensive comparison of studies without obtaining the original references. As there is no commentary to the table of 10 studies, it is difficult to interpret the results of the studies.

The 10 studies from which data have been extracted are heterogeneous in terms of treatment (first-line and second-line treatments), type of evaluation (full economic evaluations and partial economic evaluations) and type of study

(empirical cost effectiveness study, review of cost-effectiveness studies). Only two of the included studies appear to be full economic evaluations which are relevant to the UK National Health Service (NHS). Both of these studies assess the cost-effectiveness of docetaxel versus best supportive care (BSC).

As none of the papers compared erlotinib with docetaxel, these studies are not directly comparable with the economic evaluation presented in the company submission.

Quality Assessment

The submission states that descriptions of any shortcomings in the included papers will be reported. However, it is not clear from the data extraction table if this has been carried out. No formal quality assessment of the included papers is reported.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical

experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The manufacturer presented an economic analysis of the cost effectiveness of erlotinib compared with docetaxel. The analysis was based on a three-stage Markov model, with the following health states: progression-free survival, disease progression and death.

The manufacturer's base-case analysis resulted in erlotinib dominating docetaxel (that is, it was less costly and more effective). The manufacturer's probabilistic sensitivity analysis resulted in a maximum incremental cost-effectiveness ratio (ICER) of approximately 8000 pounds sterling per quality-adjusted life year (QALY) gained and a probability of 68% that the ICER was less than 30,000 pounds sterling per QALY gained.

The Evidence Review Group (ERG) reviewed the method used by the manufacturer to derive health-related utility estimates. The ERG stated that the estimates were inappropriate as they were obtained using a visual analogue scale, which was not adjusted to reflect death as having a zero utility, and were therefore not suitable for calculating QALYs. Incorporating the ERG's health-related utility estimates into the manufacturer's model reduced the final QALY gain for erlotinib from 0.0304 to 0.0182, compared with docetaxel.

Incorporating these cost and health-related utility changes, the ERG noted that the ICER would increase to approximately 52,100 pounds sterling per QALY

gained. Additional exploratory analyses conducted by the ERG showed that the ICER ranged from 31,300 pounds sterling to 70,400 pounds sterling per QALY gained depending upon the choice of health-related utility measure, the acquisition cost of docetaxel and the impact of reducing the number of cycles of chemotherapy. When also taking into account uncertainties surrounding the data on overall survival and progression-free survival, the ERG noted the possibility that docetaxel would dominate erlotinib (that is, be less costly and more effective).

The Committee concluded that in patients who were eligible for docetaxel, erlotinib should be considered as a treatment option under the arrangements of equal overall treatment costs.

Refer to Sections 3 and 4 of the original guideline document for details of the economic analyses provided by the manufacturer, the ERG comments, and the Appraisal Committee considerations.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

1. Erlotinib is recommended, within its licensed indication, as an alternative to docetaxel as a second-line treatment option for patients with non-small-cell lung cancer (NSCLC) only on the basis that it is provided by the manufacturer at an overall treatment cost (including administration, adverse events and monitoring costs) equal to that of docetaxel.
2. The decision to use erlotinib or docetaxel (as outlined above) should be made after a discussion between the responsible clinician and the individual about the potential benefits and adverse effects of each treatment.
3. Erlotinib is not recommended for the second-line treatment of locally advanced or metastatic NSCLC in patients for whom docetaxel is unsuitable

(that is, where there is intolerance of or contraindications to docetaxel) or for third-line treatment after docetaxel therapy.

4. People currently receiving treatment with erlotinib, but for whom treatment would not be recommended according to the section above, should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of erlotinib for the treatment of non-small-cell lung cancer (NSCLC)

POTENTIAL HARMS

Side effects of erlotinib treatment include diarrhea, rash, anorexia, gastrointestinal bleeding, liver-function test abnormalities and keratitis.

For full details of side effects and contraindications, see the summary of product characteristics (SPC) available at http://emc.medicines.org.uk/.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

- The Healthcare Commission assesses the performance of National Health Service (NHS) organizations in meeting core and developmental standards set by the Department of Health in "Standards for better health" issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by the National Institute for Health and Clinical Excellence (NICE) technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- "Healthcare Standards for Wales" was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires local health boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- NICE has developed tools to help organisations implement this guidance (listed below). These are available on the NICE website (www.nice.org.uk/TA162) (see also the "Availability of Companion Documents" field).
    - Audit support for monitoring local practice
    - A costing statement explaining the resource impact of this guidance

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides
Resources

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Erlotinib for the treatment of non-small-cell-lung cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Nov. 26 p. (Technology appraisal; no. 87).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Nov

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Professor David Barnett, Professor of Clinical Pharmacology, University of Leicester; Dr David W Black, Director of Public Health, Chesterfield PCT; Dr Carol Campbell, Senior Lecturer, University of Teesside; Professor Mike Campbell, Professor of Medical Statistics, University of Sheffield; Professor David Chadwick, Professor of Neurology, Liverpool University; Dr Peter Clark, Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Merseyside; Ms Jude Cohen, Chief Executive, Women's Nationwide Cancer Control Campaign; Dr Christine Davey, Senior Researcher, North Yorkshire Alliance R&D Unit; Dr Mike Davies, Consultant Physician, Manchester Royal Infirmary; Mr Richard Devereaux-Phillips, Public Affairs Manager, Medtronic Ltd; Dr Rachel A Elliott, Lord Trent Professor of Medicines and Health, Nottingham University; Mrs Eleanor Grey, Lay member; Dr Dyfrig Hughes, Reader in Pharmacoeconomics, Centre for Economics and Policy in Health, Bangor University; Dr Catherine Jackson, Professor of General Practice, St Andrews University; Dr Peter Jackson, Clinical Pharmacologist, Sheffield Teaching Hospitals NHS Foundation Trust; Professor Peter Jones, Pro Vice Chancellor for Research and Enterprise, Keele University; Dr Damien Longson, Consultant in Liaison Psychiatry, North Manchester General Hospital; Professor Jonathan Michaels, Professor of Vascular Surgery, University of Sheffield; Dr Eugene Milne, Deputy Medical Director, North East Strategic Health

Authority; Dr Martin J Price, Head of Outcomes Research, Janssen-Cilag Ltd; Dr Philip Rutledge, GP and Consultant in Medicines Management, NHS Lothian; Mr Miles Scott, Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust; Professor Mark Sculpher, Professor of Health Economics, University of York; Professor Andrew Stevens, Chair of Appraisal Committee C; Dr Cathryn Thomas, Senior Lecturer, Department of Primary Care and General Practice; Mr William Turner, Consultant Urologist, Addenbrookes Hospital

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Erlotinib for the treatment of non-small-cell lung cancer. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Nov. 2 p. (Technology appraisal 162). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Erlotinib for the treatment of non-small-cell lung cancer. Audit support. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008. 6 p. (Technology appraisal 162). Available in Portable Document Format (PDF) from the NICE Web site.
- Costing statement: erlotinib for the treatment of non-small-cell lung cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008. 2 p. (Technology appraisal 162). Available in Portable Document Format (PDF) from the NICE Web site.
- Erlotinib for the treatment of relapsed non-small cell lung cancer. Evidence review group report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Sep 1. 67 p. (Technology appraisal 162). Available in Portable Document Format (PDF) from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1737. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Erlotinib for non-small-cell lung cancer. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Nov. 4 p. (Technology appraisal 162). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N1738. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI Institute on May 13, 2009.

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